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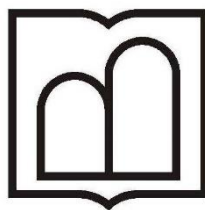
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Modeling and Intermolecular Binding Analysis of Novel 5-Aryl-1,3,4-Oxadiazole Derivatives with some Macromolecular Cancer Relevant Targets

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دانشگاه علوم پزشکی و
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سوگند نامه

اینک که برای پرداختن به پیشه داروسازی آماده هستم با ایمانی کامل و اعتقادی محکم به آفریننده بزرگ جهان هستی و کتاب آسمانی خود سوگند یاد میکنم و در پیشگاه با عظمت او پیمان می بندم و خداوند را در عهد و میثاقی پایدار خود شاهد و گواه می گیرم که در این امر خطیر همواره در راه راست و درست انسانی گام بردارم و عزت و حرمت طبابت و مصلحت بیماران و رنجوران را بر هر چیزی برتر بدانم و در برابر فریب هوای نفس از جاده صلاح منحرف نشوم و به هرکاری که با راه و رسم الهی و آئین پرهیزکاری و شرافت انسانی و پزشکی مغایرت دارد دست نیازم. قسم یاد میکنم اسرار بیماران را محفوظ و هرگز داروهایی که موجب مرگ انسان ها و یا سقط جنین می گردد در اختیار افراد جامعه نگذارم. همواره خواهم کوشید بخاطر مسائل مادی بیماران را از خدمات پزشکی و دارویی محروم نسازم تا با روی گشاده و وجدانی آزاد در پیشگاه خداوند بلند مرتبه حاضر شوم.

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Abstract

Introduction: Cancer, the uncontrollable growth of abnormal cells, is the second leading cause of death following cardiovascular diseases. Further progression of basic sciences and introduction of novel drug design techniques and possibility of predicting ligand-receptor interactions, has led to more attempts to discover, design and develop new anticancer chemicals with the hope of accessing to new drugs to complete the cancer treatment process. 1,3,4-Oxadiazole derivatives due to their unique chemical structure and biological/pharmacological applications, are known as one of the centers of attention in medicinal chemistry.

Materials, Instruments and Methods: A few novel previously synthesized 2,5-disubstituted 1,3,4-oxadiazole derivatives (**1-17**) were subjected to combined systematic docking/quantum mechanical studies against certain previously proven chemotherapeutic receptors. AutoDock4.2 and ORCA quantum chemistry packages were used for modeling studies while LigPlot and Viewer Lite software were applied for obtaining ligand-target binding patterns.

Results and Discussions: In the current project, it was tried to explore binding modes/affinities of experimentally validated 1,3,4-oxadiazoles (**1-17**), to some validated chemotherapeutic targets. Structure binding relationship (SBR) studies showed that chemical structures possessing halogen atoms on 5-substituted phenyl and *N*-benzyl rings (**4** and **17**) exhibited superior binding modes/energies with regard to the majority of studied targets, regardless of their cytotoxic activity. A few oxadiazole structures exhibited ΔG_b s comparable to or stronger than crystallographic ligands that were previously demonstrated to inhibit intended targets. On the basis of obtained results, a general SAR/SBR for binding of candidate oxadiazoles to binding sites of relevant targets was developed and a few top-ranked 2,5-disubstituted 1,3,4-oxadiazole structures were proposed as potential cytotoxic candidates that were also virtually validated. Moreover; lowest binding energy in the B3LYP/Def2-SVP level of calculation could be estimated for Arg486 (-6.05 kcal/mol) in binding of compound **17** to telomerase.

Conclusion and Suggestions: Various studies have demonstrated 1,3,4-oxadiazole heterocyclic nucleus as a privileged medicinal scaffold. A series of novel 2,5-disubstituted 1,3,4-oxadiazole derivatives were elucidated for their intermolecular binding patterns with some of the cancer relevant oxadiazole-inhibited targets. On the basis of obtained results, a general SAR/SBR pattern for candidate 1,3,4-oxadiazoles was offered and some hybrid oxadiazole structures were proposed as potential cytotoxic agents. Since the assessed macromolecular targets were previously proved to be blocked by 1,3,4-oxadiazoles, the results of this study might be useful in further design of more potent anticancer 1,3,4-oxadiazole derivatives through extending the scope of privileged structures toward designing new potential anti-tumor compounds.

Keywords

Cancer; Cytotoxicity; Oxadiazole; Docking; Quantum Mechanical

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Signs and Abbreviations

ADT: AutoDock Tools
BCL-2: B Cell Lymphoma-2
CADD: Computer-Aided Drug Design
EGF: Epidermal Growth Factor
FAK: Focal Adhesion Kinase
FAS: Fatty Acid Synthase
GSK-3: Glycogen Synthase Kinase-3
HAC: Heavy Atom Count
HBA: H-bond Acceptor
HBD: H-bond Donor
HDAC: Histone Deacetylase
hTRT: human Telomerase Reverse Transcriptase
IUPAC: International Union of Pure and Applied Chemistry
LE: Ligand Efficiency
MetAP: Methionine Aminopeptidase
SAR: Structure Activity Relationship
SBR: Structure Binding Relationship
PKB: Protein Kinase B
PDB: Protein Data Bank
QM: Quantum Mechanical
RMSD: Root Mean Squared Deviation
RTB: Rotatable Bond
TS: Thymidylate Synthase
VEGF: Vascular Endothelial Growth Factor
WHO: World Health Organization
Å: Angstrom
 E_b : Electronic Binding Energy
 G_b : Binding Free Energy
 K_i : inhibition Constant

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